PATENT
Docket No. 511582001620

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Tami M. Procopio

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Daniel E. AFAR, *et al.*

Serial No.: 09/455,486

Filing Date: 6 December 1999

For: NOVEL SERPENTINE TRANSMEMBRANE ANTIGENS EXPRESSED IN HUMAN CANCERS AND USES THEREOF

Examiner: Gary B. Nickol, Ph. D.

Group Art Unit: 1642

PRELIMINARY COMMUNICATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Communication and Declaration further accompany the Request for Continued Examination filed herein on 24 December 2003. These documents respond to the issues raised in the Advisory Action mailed 2 October 2003.

First, as a preliminary statement, it has been established by declaratory evidence that the STEAP-2 protein claimed is indeed produced as a protein and that thus the expression data based on messenger RNA are indicative of protein production. This was established by the expert declaration of Mary Faris submitted on 3 June 2002. This declaration demonstrated that cells transfected with an expression system for STEAP-2 showed:

1. enhanced tyrosine phosphorylation levels;

2. enhanced phosphorylation of ERK;

3. enhanced calcium ion flux;

4. increased sensitivity to calcium ion channel blockers; and

5. enhanced resistance to paclitaxel.

All of these effects, which were demonstrated experimentally, are dependent on the production of protein. Further, a modified form of STEAP-2 with altered conformation due to a fusion with a flag sequence fails to show these effects. The cells used to demonstrate these effects were themselves cancer cells, so that it is clear that there is no barrier to translation of produced messenger RNA in cancer cells. This is the expert opinion of Mary Faris.

Applicants note that in the Advisory Action, the Examiner asserts that the

> [Greatly] increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a simple extrapolation of *in vitro* assays to human "diagnostic" efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell/cell interactions that may be important in a particular pathological state. Furthermore, it is well known in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type.

None of this is supported by any evidence or is probative of any assertion that the production of protein from messenger RNA in transfected cancer cells would not reflect the production of protein from messenger RNA in cancer cells *in situ*. There is no rational basis provided to assume that the cancer cells *in vivo*, because of cell/cell interactions or any other phenomenon, would fail to express the protein. Respectfully, applicants believe that the evidence provided and authenticated by an expert in the field has not been impugned by the Office.

The Office states that the specification provides neither guidance on nor exemplification of how to correlate STEAP-2 protein expression with the ability to provide a diagnostic

evaluation of an oncogenic disorder. This is not the case. For example, on page 20 of the specification, lines 11-22, it is explicitly stated that antibodies immunoreactive with the STEAP proteins can be used to detect, monitor and establish a prognosis of prostate cancer, particularly advanced prostate cancer; lines 29-34 indicate that other cancers that express STEAP, such as breast cancer can be diagnosed in this manner. The association of STEAP-2 expression with cancer as opposed to normal tissue expression is documented in the enclosed Declaration of Dr. Pia M. Challita-Eid which utilizes controlled semi-quantitative PCR to demonstrate enhanced expression. See, *e.g.*, Exhibit 3. A variety of cancers is shown to express STEAP-2 in contrast to its lack of expression in normal tissues. Thus, there can be no question that STEAP-2 protein is useful in generating antibodies that can be used to detect cancerous tissue.

The Examiner asserts that the use of STEAP-2 as a marker for metastatic disease is "speculative at best." However, this use, too, is supported by the expert Declaration of Karen Morrison filed 29 July 2003 and also of record. Evidence is already in the specification as indicated in Dr. Morrison's declaration that most normal tissue does not contain expressed STEAP-2. Page 10, lines 12-18 discuss the typical metastatic sites for prostate cancer. It is not speculative, therefore, to conclude that the presence of STEAP-2 expression at locations typical of metastasis of prostate cancer are useful in diagnosis of this metastasis.

Further, as noted in Dr. Morrison's declaration, indications of "overexpression" in tumor tissues is not the only criterion for utility of this protein as a marker. As noted in paragraph 12 of her declaration, the availability of antibodies to STEAP-2 makes it possible to determine the intracellular location of this protein, and thus to detect abnormalities in this intracellular location as well as to determine the susceptibility of the cell surface to treatment with antibodies.

Further, the Examiner asserts that STEAP-2 has no utility as a screening tool. The specification clearly contemplates this use on page 12, line 32-page 13, line 22. The assertion

that this protein can serve as an ion channel is clearly supported by declaratory evidence already submitted by Mary Faris on 29 July 2003. Thus, the description in the specification is supported by data. The Office provides no support for its assertion that results obtained in cultured cells are irrelevant to the use of this protein as a screening tool. There is an expert declaration of record to the contrary.

In addition to the documentation already of record and the expression data set forth in the enclosed declaration, applicants submit additional evidence that the protein claimed is detectable by immunological assay, and is detectable in cancer tissue by such assays. The enclosed Declaration of Dr. Challita-Eid also demonstrates that (a) antibodies are successfully raised that immunoreact with STEAP-2 protein, (b) STEAP-2 protein is produced in cancer cells in a form detectable by these antibodies, and (c) patient cancer specimens contain STEAP-2 protein detectable with these antibodies.

Aside from the obvious utility of the STEAP-2 protein to produce antibodies which can be used as markers in diagnostics for tumors and metastases, the antibodies elicited by this protein have therapeutic utility as well. Since the prostate is a non-essential organ, direct administration of antibodies immunoreactive with STEAP-2 protein, demonstrably expressed at high levels in prostate tumors provides an entirely credible approach to inactivating this protein in the prostate. Even if STEAP-2 is present in the normal surrounding tissue, this is irrelevant to the efficacy of the treatment since the prostate is itself a dispensable organ. The data supplied in Dr. Challita-Eid's declaration clearly demonstrate that STEAP-2 protein immunoreactive with antibodies raised by this protein is present at high levels in both prostate cancer (and lung cancer – adenocarcinoma).

In light of the plethora of data supplied by applicants demonstrating that STEAP-2 protein is useful as a screening tool, as a marker for detecting cancer, and to produce antibodies

as candidate therapeutic agents, applicants believe the claims meet the requirements of the statute. Applicants understand that the rejection is made under 35 U.S.C. § 112, paragraph 1, asserting a lack of written description or enablement. However, the specific locations of written descriptions of the uses provided by applicants has been shown in the specification; there can be no question of enablement as those skilled in the art clearly know how to raise antibodies, to detect protein using antibodies and to use proteins as screening tools to identify molecules that interact with them, as well as to provide antibodies directly to a tumor, *e.g.*, prostate, as suggested on page 30 of the specification. Accordingly, the rejection is properly cast as a rejection for lack of utility; in this regard, applicants have shown that the utilities provided are credible, substantial, and specific.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 511582001620.

Respectfully submitted,

Dated: February 10, 2004 By: Kate H. Murashige

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